Interdependence of Atrial Fibrillation and Heart Failure With a Preserved Ejection Fraction Reflects a Common Underlying Atrial and Ventricular Myopathy

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ON MY MIND

Interdependence of Atrial Fibrillation and Heart Failure With a Preserved Ejection Fraction Reflects a Common Underlying Atrial and Ventricular Myopathy

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Atrial fibrillation (AF) and heart failure with a preserved ejection fraction (HFpEF) are closely intertwined disorders that afflict millions of people, many of whom are obese or have diabetes mellitus or other proinflammatory conditions. Conceivably, the convergence of AF and HFpEF might be explained by 2 distinctly different frameworks. On the one hand, it is possible that each phenotype might lead sequentially to the other (ie, the increased left ventricular [LV] filling pressure in HFpEF may cause left atrial [LA] dilatation that triggers AF, and conversely, the rapid heart rate that accompanies AF might lead to LV fibrosis, although there is little evidence to support this hypothesis). On the other hand, and more likely, the 2 disorders may be parallel manifestations of the same underlying myocardial disease, which causes AF (because it affects the LA) and HFpEF (because it afflicts the LV).

EPIDEMIOLOGICAL AND CLINICAL INTERDEPENDENCE OF AF AND HFPEF

Epidemiological studies demonstrate a strong link between AF and HFpEF. AF is one of the primary precedents and predictors of the development of HFpEF; conversely, most patients with HFpEF are destined to develop AF, if the arrhythmia is not already evident.[1] The convergence of AF and HFpEF is underestimated, because unrecognized AF occurs years before patients are given a diagnosis, and patients experience exertional dyspnea long before physicians identify the presence of heart failure. Patients who present with AF (but without a diagnosis of HFpEF) commonly have increased LV filling pressures by invasive or noninvasive assessment, especially if they have exercise intolerance.[2] The evolution and progression of AF and HFpEF are so strikingly parallel that the determination of which disorder came first may be a matter of diagnostic diligence, rather than a reflection of a causal sequence from 1 disorder to the other.

MECHANISTIC INTERDEPENDENCE OF AF AND HFPEF

The pronounced epidemiological and clinical parallelism of AF and HFpEF supports the existence of a common mechanistic substrate for the 2 diseases. Interestingly, in the general community, biomarkers of systemic inflammation and fibrosis precede and predict AF as well as HFpEF and are associated with both abnormalities in diastolic filling and exercise intolerance.

Why does systemic inflammation lead to both AF and HFpEF? Endothelial inflammation can cause coronary microvascular dysfunction and fibrosis, which can induce both an atrial and a ventricular myopathy. In addition, systemic inflammatory and metabolic disorders have been linked to an expansion and proinflammatory

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transformation of epicardial adipose tissue. By its proximity to the myocardium, epicardial fat may act as an amplifier, intensifying the ongoing systemic inflammatory process and focusing it onto the underlying tissues.[3] If the epicardial adipose tissue inflammation were to influence the atria, the expected result could be electroanatomical fragmentation and LA mechanical dysfunction, with or without AF. If epicardial adipose tissue inflammation were directed to the LV, the resulting coronary microvascular dysfunction might impair the ability of the LV to accommodate blood volume unless filling pressures increased disproportionately; such decreased LV distensibility represents the hallmark of HFpEF. Epicardial adipose tissue mass is expanded in patients with AF, particularly if they have systemic inflammation or are at high risk of adverse outcomes, and epicardial adiposity is particularly prominent in patients with HFpEF who have AF.

LA remodeling is central to the pathogenesis of both AF and HFpEF. Whereas the LA in patients with heart failure and a reduced ejection fraction is typically enlarged with increased distensibility, LA reservoir function is diminished in patients with HFpEF. Accordingly, patients with heart failure and a reduced ejection fraction have larger LA volumes but lower peak LA pressures, whereas those with HFpEF have greater LA stiffness leading to smaller (although still enlarged) LA volumes despite higher peak pressures. Yet, despite the lesser degree of LA dilatation, patients with HFpEF are more likely to have AF, suggesting that atrial fibrosis (not chamber distension) is the primary determinant of AF in HFpEF. The increases in LA pressures seen in HFpEF and AF may not be simply related to the retrograde transmission of LV end-diastolic pressures, but instead reflect the hemodynamic consequences of the underlying atrial myopathy. Whereas the pulmonary wedge pressure is typically lower than the LV end-diastolic pressure in patients in sinus rhythm, the opposite is true in patients with left heart disease and AF. Furthermore, when compared with LV diastolic filling patterns, measurements of LA strain (reflecting severity of atrial myopathy) are superior in identifying HFpEF and are more closely related to exercise capacity and outcomes in these patients.

INTERDEPENDENCE OF AF AND HFPEF ON FUNCTIONAL CAPACITY AND OUTCOMES

In patients with AF, abnormalities of diastolic filling are accompanied by exercise intolerance; conversely, in HFpEF, AF is linked to greater degrees of functional impairment, but this is not related to exercise-induced tachycardia. Patients with both AF and HFpEF who have greater functional capacity have higher exercise heart rates. Furthermore, the slowing of heart rate in sinus rhythm may have deleterious effects in patients who have HFpEF, because prolongation of diastole may enhance filling in a LV that is already overfilled.[4] Therefore, the association of AF and effort intolerance in HFpEF appears to be driven primarily by LA and right ventricular dysfunction, which are common in patients with AF and can each limit exercise performance.

Patients with HFpEF or AF are at increased risk of stroke, particularly when both conditions are present. This synergism exists even when HFpEF has not been formally identified (ie, patients with AF who have diastolic filling abnormalities are predisposed to thromboembolic events). Decreased LA flow velocity (attributable to atrial myopathy) and enhanced thrombogenicity of the fibrotic atrial endocardium increase the liability to thromboembolization. In fact, atrial fibrosis is independently associated with LA thrombus formation and the risk of stroke, even without AF or LA dilatation. Importantly, at-risk patients generally do not exhibit AF preceding a stroke, and a diagnosis of HFpEF increases the likelihood of a subclinical cerebral infarction in patients without AF. Therefore, the severity of LA disease may be the primary determinant of vascular brain injury.[5]

In longitudinal studies, the development of AF after the diagnosis of HFpEF increases the risk of death, and patients who develop HFpEF after the diagnosis of AF also have a worse outcome. These relationships may reflect the fact that patients with both AF and HFpEF have a more advanced stage of the underlying myopathy than patients with only AF or only HFpEF. However, any evaluation of the independent prognostic importance of concurrent AF and HFpEF on morbidity and mortality is complicated by the fact that HFpEF is often the reflection of a systemic inflammatory or metabolic disorder, which exerts its own independent influence on the risk of end-organ dysfunction and adverse clinical outcomes as well as on the development of AF.

CONCLUSIONS

AF and HFpEF demonstrate an exceptionally high degree of clinical and epidemiological convergence. Regardless of which disorder presents first, both are or will soon become evident in the same patients. AF and HFpEF appear to both be manifestations of a common underlying atrial and ventricular myopathy that is triggered when a systemic inflammatory or metabolic disorder causes coronary microvascular dysfunction and fibrosis of the atrial and ventricular myocardium, a process that may be mediated or exacerbated by inflammation in the adjoining epicardial adipose tissue.

ARTICLE INFORMATION

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Disclosures

Dr Packer has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, WebMD Global LLC, Radcliffe Group Ltd, and Corpus. Dr Lund is a Swedish Research Council Clinical Scientist and additionally supported by the Swedish Heart-Lung Foundation and Erling Persson Family Foundation. Dr Lund reports personal fees from Merck, grants from Boehringer Ingelheim, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, grants and personal fees from Novartis, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, and personal fees from Medscape, outside the submitted work. Dr Redfield has provided consulting to Novartis and Ironwood (but with no personal compensation).

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